Dietary intervention in rheumatoid arthritis

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Rheumatoid arthritis is a disabling disease prevalent in modern society. Dietary prevention may be possible in a subgroup of individuals who appear to suffer food intolerance; dietary intervention, as an adjunct to other management strategies, may be useful in modifying the inflammatory response. The former suggestion is supported by anecdotal evidence; the latter by some in vitro experimentation which implicates arachidonic acid metabolism in the pathogenesis of rheumatoid tissue inflammation. While the value of dietary modification in the prevention and control of rheumatoid arthritis remains unproven, the potential benefits are significant. Further clinical investigation is justified. In the interim dietary modification which takes congnisance of arachidonic acid metabolism can be justified provided this falls within general dietary recommendations for modern society.

KEY WORDS: rheumatoid arthritis, diet, arachidonic acid, prostaglandins, food intolerance, chiropractic

L'arthrite rhumatoïde est une maladie débilitante courante dans la société moderne. Une prévention d'ordre diététique est possible pour une sous-groupe d'individus qui semblent souffrir d'une intolérance alimentaire; une intervention diététique, associée à d'autres stratégies de traitement, peut s'avérer utile en modifiant la réponse inflammatoire. La première suggestion s'appuie sur des évidences anecdotiques; la seconde suggestion s'appuie sur des expériences in vitro qui impliquent le métabolisme de l'acide arachidonique dans la pathogénèse de l'inflammation du tissus rhumatismal. Alors que la valeur d'une modification diététique pour la prévention et le contrôle de l'arthrite rhumatoïde reste non prouvée, les bénéfices potentiels en sont considérables. Une investigation clinique supplémentaire est justifiée. En attendant, des modifications diététiques tenant compte du métabolisme de l'acide arachidonique peuvent être justifiées, pour autant qu'elles recoupent les recommandations diététiques générales d'une société moderne.

MOTS CLÉS: arthrite rhumatoïde, régime diététique, acide arachidonique, prostaglandines, intolérance alimentaire, chiropratique

Introduction

Rheumatoid arthritis is an important chronic degenerative disease in modern society. The disease is more prevalent in the older age groups. We live in an aging society and it has been suggested that up to 80% of persons of retiring age have some rheumatic complaint.[1] The prevalence of rheumatoid arthritis in the United States is currently between 3.0 and 0.25% of the total adult population[2]; but increases are predicted. The assessed incidence varies according to the diagnostic criteria used.

The American Rheumatism Association uses an eleven point diagnostic table which includes[3]:

- morning joint stiffness*, which is present in two thirds of cases;
- joint tenderness* or pain precipitated by movement* affecting one or more joints;
- soft tissue thickening* or effusion* of one (score one) or more (score two) joints;
- symmetrical joint swelling*; except for distal interphalangeal joint swelling;
- subcutaneous nodules;
- typical radiological changes; X-rays are usually normal in the early stages of the disease;
- serology positive for rheumatoid factor;
- synovial fluid which demonstrates poor mucin clotting;

* These findings score when present continuously for six or more weeks.

- characteristic changes of synovium (score one) and/or subcutaneous nodule(s) (score one) on histology.

According to this classification, rheumatoid arthritis is probable when three signs are present; definite when five and classical when seven criteria are present. More specific classifications which have positive serology as a prerequisite to diagnosis are prone to underestimate the incidence of rheumatoid arthritis. A positive rheumatoid factor is more useful as a diagnostic than screening criterion. It is more often absent than present in the early stages of the disease and remains negative in one in ten diagnosed cases.

Despite modern technology the diagnosis of early rheumatoid arthritis depends on clinical assessment.[4] Despite contemporary disease intervention, rheumatoid arthritis is neither amenable to prevention nor cure. Rheumatoid arthritis challenges the management skills of conscientious clinicians and lures the uncritical along pathways of fads and folklore. Nutritional intervention is one such potentially hazardous pathway.

Dietary modification in the prevention of rheumatoid arthritis

Primary disease prevention becomes feasible when the aetiology of a disease is both identifiable and avoidable. Research has yet to clearly define the aetiology of rheumatoid arthritis. It is suspected that persons with a genetic predisposition to rheumatoid arthritis may respond to particular infections or other immune system triggers by initiating those inflammatory changes which regularly emerge during the pathogenesis of the disease.[5] Certain workers have suggested that food intolerance may, in a certain group of patients, constitute an immune trigger.[6]

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Food intolerance

Type I (reaginic), type III (immune complex) and type IV (cellmediated) hypersensitivity have all been linked with food allergy.[7] At least one of these reactions has been regularly implicated in rheumatoid arthritis. Immune complexes have been clearly established as a basic element in the pathogenesis of this disease.[8] The classic clinical triad of food allergy is however currently confined to dermatological, gastro-intestinal and respiratory manifestations – it does not at present extend to incorporate joint lesions. A more contemporary view of food intolerance which does not adhere to the traditional criteria of food allergy does recognise arthralgia and arthritis as a potential outcome of chronic exposure to an allergen in an individual with cyclic food allergy.[9] Certainly anecdotal evidence and a limited number of case studies do suggest that this possibility should be seriously considered.[10] Should this latter hypothesis be appropriate for at least a subgroup of rheumatoid arthritis sufferers, then dietary modification in these patients is a clinically justifiable management strategy.

It is interesting to note that dietary management to avoid intestinal allergen exposure may not only be a logical intervention against an aetiological factor in rheumatoid arthritis; it may also be implemented to minimize the risks of exacerbations in patients on drug therapy. Arthritic patients on non-steroidal anti-inflammatory drugs have been shown to have increased intestinal permeability.[11] Identification of, and dietary management to avoid, food allergen exposure may constitute a valid clinical strategy in appropriate patients.[12] Early recognition of mucosal barrier malfunctions[13] complemented by identification of allergic foodsubstances in susceptible individuals may someday constitute a preventive approach to rheumatoid arthritis.

Dietary intervention in the treatment of rheumatoid arthritis

In addition to avoiding ingestion of personally identified food allergens, dietary management may be implemented in an attempt to modify the pathogenesis of the disease. This approach diverges from the specific approach which identifies an idiosyncratic response to an allergen, and focuses instead on altering cellular constituents so as to minimize inflammation.

The pathogenesis of rheumatoid arthritis:

Histological changes accompanying the clinical manifestations of rheumatoid arthritis include proliferation of synovial lining cells and joint infiltration by lymphocytes, plasma cells, macrophages and polymorphs. In time an ingrowth of granulation tissue over the perichondral margins spreads to form a pannus over the articular surfaces with consequent progressive joint deformity. Biochemical changes underlying these microscopic changes are believed to involve the products of arachidonic acid metabolism.

The products of arachidonic acid metabolism enhance the humeral and cellular response in inflammation and modify the local immune response. Arachidonic acid when exposed to cyclo-oxygenase generates prostaglandins of the 2 series; following exposure to lipo-oxygenase, arachidonic acid derivatives are the leukotrienes-4 ie, those leukotrienes with four double bonds. Both these products, to varying degrees, increase inflammation. Leukotrienes promote leucocyte chemotaxis, enhance release of lysosomal enzymes, increase vascular permeability and are markedly proinflammatory. Members of the prostaglandin 2 series include thromboxanes, prostacyclin and prostaglandin E2. Depending on the tissue involved the major product of arachidonic acid metabolism may be, as in platelets, thromboxanes which stimulate platelet aggregation and vasoconstriction or, as in the arterial wall, prostacyclins which inhibit platelet aggregation and relax the musculature of the arterial wall.[14] In the rheumatic joints of arthritic patients, the third major product of cyclo-oxygenase metabolism of arachidonic acid, prostaglandin E2 (PGE2), is of great importance. This compound has been shown, at low concentrations, to cause erythema and potentiate the oedema and pain resulting from inflammatory mediators such as bradykinin and histamine.[15] At physiological concentrations PGE2 has, in vitro, been shown to suppress T-lymphocyte functions and inhibit the cytotoxicity of non-T lymphocytes. In fact it has been hypothesised that endogenous production of PGE2, through tonic inhibition of suppressor cell activity, by enhancing autoantibody production results in accumulation of rheumatoid factor in affected joints.[16] Certainly, owing to the short-half life of PGE2, this compound's activity is largely limited to its site of production. Regardless of whether the major effect of PGE2 is via its influence on the immune system or due to its direct, or more importantly indirect, pro-inflammatory effect, it has been noted that a high concentration of cyclo-oxygenase derived products are associated with enhanced inflammation in a joint; reduction of these products is followed by reduced inflammation.[17]

Arachidonic acid – accomplice in the pathogenesis of rheumatoid arthritis:

A tentative model linking rheumatoid arthritis and arachidonic acid metabolism has been proposed.[18] This model suggests that the macrophages and leucocytes which infiltrate the synovium increase the joint's concentration of prostaglandin-E2, thromboxane and leukotriene-4's. These products assisted by activated fragments of complement further stimulate the influx of leukocytes which in turn aggravate inflammation by enhancing chemotaxis and local vascular permeability. Prostaglandin E2 is perceived as a particular villain as it is believed to also mediate bone resorption by increasing osteoclast numbers, to stimulate collagenase secretion by macrophages and to inhibit proteoglycan production by synoviocytes and articular chondrocytes. In vitro experimentation, with cultures of rheumatoid synovial tissue, supports the view that prostaglandins play a substantial role in the development of the cartilagenous lesion in inflammatory arthritis .[19,20] Injured tissue generates inflammatory prostaglandins, chemotaxed leukocytes release prostaglandins during phagocytosis while macrophages, the dominant cell in chro-

nic inflammation, also produce prostaglandins. The inflammatory cycle is self perpetuating.

Additional support for the central role of arachidonic acid metabolites in the pathogenesis and clinical presentation of rheumatoid arthritis may be gained from an examination of the mechanisms whereby anti-inflammatory agents are believed to achieve a clinical response in arthritic patients. Salicylates and non-steroidal anti-inflammatory drugs, initially alone and later in combination, are the first and second line drug therapies recommended by certain rheumatologists.[21]

The manner in which these drugs exert their anti-inflammatory effect, while somewhat disputed depending on the researcher's training, does tend to emphasize inhibition of the synthesis of prostaglandins.[22] It has been suggested that the immediate symptomatic relief of chronic inflammation is the result of blocking cyclo-oxygenase metabolism; a more permanent effect may only be achieved on inhibiting lipo-oxygenase. Corticosteroids impair release of arachidonic acid from cell membranes thereby effectively inhibiting the synthesis of products via the lipo-oxygenase and cyclo-oxygenase pathways.[23] Clinically, steroids are regarded as more effective than the drugs mentioned – they are however used with greater caution due to increased side effects. Histological evidence and the clinical response to anti-inflammatory agents support the hypothesis that arachidonic acid metabolism may be involved in the pathogenesis of rheumatoid arthritis.

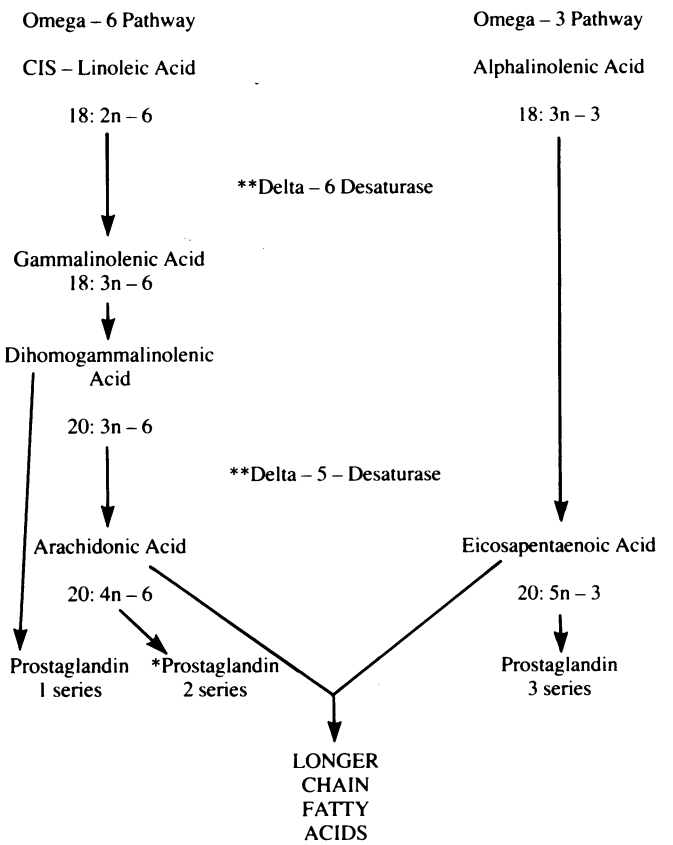
Dietary intervention:

Certain workers have suggested that dietary manipulation which alters cellular arachidonic acid may have a beneficial effect in the management of rheumatoid arthritis. Arachidonic acid is found as a component of cell membranes. The major cellular components of arachidonic acid appear to be esterified in membrane phospholipids and to a lesser extent in triglycerides and cholesterol esters. Cellular arachidonic acid is derived from the diet. Once considered an essential fatty acid, it is now recognised that linoleic acid is an arachidonic acid precursor. These fatty acids are both omega-6 fatty acids. Both of these omega-6 fatty acids, along with omega-3 fatty acids, can act as precursors of prostaglandins. Prostaglandins, depending on the series, may enhance or retard inflammation; while their role as intracellular regulators of metabolism includes temperature modification, platelet aggregation, vascular contraction and modulation of the immune response.

Important dietary sources of the omega-6 fatty acids (ie. of arachidonic acid) are animal tissues, and of linoleic acid are vegetable oils. Safflower seed oil contains over 70% linoleic acid while there is a concentration of about 50% of this essential fatty acid in soyabean, corn and cottonseed oils. Barley, wheat and apples are also good sources of linoleic acid. In vivo conversion of linoleic acid to arachidonic acid depends on the presence of two desaturase enzymes. Delta6-desaturase converts linoleic acid to gamma-linolenic acid, the precursor of dihomogamma-linolenic (DHLA) (Figure 1). DHLA may be converted into arachidonic acid or it may generate prostaglandins of the 1 series. Substrate competition for this rate limiting enzyme in arachidonic acid synthesis may also occur from omega-3 fatty acids. While linoleic and arachidonic acids are omega-6 fatty acids; alpha-linolenic acid is an omega-3 fatty acid. Alpha-linolenic acid is the precursor of eicosapentaenoic acid (EPA), the substrate for the synthesis of the 3-series of prostaglandins (Figure 1). Prostaglandins of both the 1- and 3-series lack the pro-inflammatory activity of prostaglandins of the 2 series. Alteration to the substrate or activity of these desaturase enzymes may therefore, in theory, modify the local inflammatory response.

Dietary manipulation may achieve alterations in these enzymes activity. Delta6-desaturase is thought to be the rate limiting enzyme in these reactions. Fasting, glucose, fructose, glycerol, linoleic and arachidonic acids all suppress delta6-

Figure 1 Essential fatty acid catabolism.



* Prostaglandins of the 2 series are more pro-inflammatory than those of the 1 and 3 series.

** Desaturase enzymes have a greater affinity for Omega-3 than Omega-6 fatty acids.

desaturase activity; protein rich or essential fatty acid deficient diets activate this enzyme.[24] Linolenic acid competes successfully with linoleic acid for delta6-desaturase. Dietary sources of alpha-linolenic acid are linseed oil, spinach, beans and aquatic plants.

In addition to attempting to alter the qualitative production of prostaglandins by targeting desaturase enzyme activity it is also possible to enhance production of the prostaglandin-3 series by supplementing the diet with foods rich in omega-3 fatty acids. Cod, mackerel, herring, crab, shrimps and oysters along with other cold water fish and evening primrose oil are sources of EPA. Such a dietary change from omega-6 to omega-3 fatty acid sources is postulated to reduce the production of the pro-inflammatory and platelet aggregratory prostaglandin 2 series and leukotrienes. This concept has been applied clinically.

Clinical evidence of therapeutic management with omega-3 and omega-6 fatty acids:

The precipitating event in coronary occlusion is frequently a thrombosis – in coronary artery diseased patients dietary change to alter platelet aggregation by modifying prostaglandins may be recommended. It is possible that regular weekly fish eating, with or without EPA supplementation, may reduce the risk of coronary artery thrombosis.[25] Clinical investigation has futhermore shown that dietary supplementation of up to 10 grams per day with eicosapentaenoic acid can increase the EPA content of red cell and platelet phospholipids.[26] Dietary change can alter essential fatty acid metabolism; dietary supplementation can alter the patterns of synthesis of thromboxanes and prostacyclins. While there is less clinical evidence to support the role of dietary manipulation in the general management of rheumatoid arthritis, these studies have demonstrated that dietary modification can modify arachidonic acid and prostaglandin metabolism.

Critics may argue that the beneficial modification of prostaglandin metabolism in coronary artery disease does not justify any suggestion that a similar approach may be applicable in rheumatoid arthritis. The effect of prostaglandins 1 and 3 is to inhibit platelet aggregation (and therefore is of benefit in coronary artery disease); they lack any significant influence on inflammation (and therefore have no role in rheumatoid arthritis management). Modification of the essential fatty acid substrates available in the phospholipids of cell membranes in arthritic patients with consequent modification of the prostaglandin composition can still help to reduce inflammation – if merely by the reduced production of prostaglandins-2 and leukotrienes as a result of substrate competition. Furthermore, there is some clinical evidence which supports the use of omega-3 dietary supplementation as a means of reducing the inflammatory response.

It has been demonstrated that eicosapentaenoic acid and its product docosahexaenoic acid both competitively inhibit the catabolism of arachidonic acid by cyclo-oxygenase. Lee and co-workers demonstrated that by supplementing the diet with these marine oils they could alter the lipid composition of neutrophil and monocyte membranes.[27] They showed that such an alteration of monocyte and neutrophil membrane composition had an overall anti-inflammatory effect in vitro and postulated that this was attributable to suppression of the lipo-oxygenase pathway in both these cells complemented by inhibition of leukotriene B4-mediated functions in neutrophils. Incorporation of EPA into cellular membranes by dietary supplementation is postulated to inhibit the cyclo-oxygenase pathway leading to production of the prostaglandin 2 series; to produce leukotrienes that are 10–30 times less potent than those resulting from arachidonic acid catabolism by lipo-oxygenase; and to alter the function of human leukocytes.[28]

Dietary management – an unproven hypothesis:

The role of dietary manipulation in predictably influencing the pathogenesis of rheumatoid arthritis remains unproven. Controlled clinical studies are required. Further investigation into therapeutic dietary intervention in rheumatoid arthritis is justifiable in view of:

- the undisputed role of inflammation in the pathogenesis of rheumatoid arthritis;
- the proven role of metabolites of arachidonic acid in the inflammatory process;
- the experimental evidence that dietary alteration can influence the lipid composition of cell membranes; and
- the qualitative dependence of the prostaglandin and leukotriene response to tissue injury on the constituents of cellular membranes; ie the dependence of the product on its precursor.

Future clinical research into diet and rheumatoid arthritis

Ziff in his analysis of diet as a mode of therapy in rheumatoid arthritis suggested three possible scenarios for clinical trials.[29] These included:

1 The dietary elimination of polyunsaturated fatty acids with supplementation of essential fatty acids to avoid deficiency syndromes.
2 The dietary loading with selected polyunsaturated fatty acids to enhance the synthesis of suppressor type prostaglandins.
3 The dietary supplementation with eicosapentaenoic acid or adoption of the Greenland Eskimo diet.

Elimination of polyunsaturated fatty acids from the diet with supplementation of linoleic and linolenic acid is possibly the most tedious of the three alternatives suggested. Signs of essential fatty acid deficiency appear related to inadequate dietary intake of both linoleic and linolenic acids; in cats arachidonic acid deficiency may also cause problems. Linolenic acid, ie. omega-3 precursor, deficiency may result in the neurological symptoms of numbness, parasthaesia, weakness and limb pain; blurring of vision has also been reported. Linoleic acid, ie. the omega-6 precursor, deficiency results in dermatosis characterized by increased water permeability of the skin, reduced sebum production and epithelial hyperplasia; growth retardation

and changes to the lipid composition of cells have also been noted. The minimum human requirement of linoleic acid is judged to be about 1% of dietary energy; the requirement for linoleic acid is unknown.

Essential fatty acid requirements are also believed to change with age and physiological condition. The replacement dose of essential fatty acid in patients placed on such a dietary regime would therefore constitute a dilemma.

Ziff's second dietary alternative appears more conducive to clinical implementation. This diet would require that limitation should be placed on dietary sources of arachidonic acid – land animal cell membranes are rich sources; red meats should be eliminated from the diet. Dietary supplementation with foodsubstances likely to minimize in vivo arachidonic acid synthesis would accentuate omega-3 fatty acids and emphasise linoleic rather than arachidonic acid as the representative of the omega-6 series. Linseed oil, spinach, beans and fish would feature in such a diet.

Ziff's third alternative emphasises cold water fish as characterized by the Eskimo diet. It can also be achieved by dietary EPA supplementation. A diet high in polyunsaturated fats which limited saturated fats and used an EPA supplement MaxEPA was offered to seventeen patients with rheumatoid arthritis.[30] After twelve weeks on this diet the experimental group suffered less morning stiffness and joint tenderness than the controls. Two months after stopping the diet the experimental group showed clinical deterioration. It has been suggested that, rather than indicating a response to altered fatty acid metabolism, this study demonstrates unmasking of a food allergy following twelve weeks on an elimination diet.[31] Other criticisms of this work include the difficulty encountered in adequately interpreting the findings in patients with a disease which has a natural history of exacerbations and remissions and problems in appropriately interpreting clinical change.[32] Despite this, the results of this trial do support the notion that dietary manipulation deserves investigation as a mode of therapy in rheumatoid arthritis – both with regard to preventing rheumatoid arthritis (the food allergy hypothesis); and as a means of minimizing joint inflammation.

It is desirable that future clinical trials investigating the effect of diet on rheumatoid arthritis attempt to focus on specific dietary modifications. These results are likely to prove more useful than those resulting from a well designed study by Panush et al, which as the experimental diet used a "popular" intervention diet, ie. one free of preservatives, additives, red meats, dairy products, herbs and fruit.[33] While their results failed to demonstrate objective overall improvement in their experimental group, they did conclude that selected rheumatoid arthritis patients may benefit from dietary manipulation. It is possible that the two patients who notably improved on their experimental diet were food intolerant with resultant improvement on their "elimination diet"; it is also possible that their results may have been more favourable had they specifically focused on omega-3 fatty acid supplementation.

Nutritional management of patients with rheumatoid arthritis

Until such time as clinical research can provide clear guidance with regard to the use of nutritional intervention in the management of rheumatoid arthritis, it is suggested that the practitioner implement these findings in so far as they are congruent with contemporary dietary guidelines.[34,35] In general, nutritionalists recommend that developed societies curtail their fat intake, particularly that derived from animals viz meat; and increase their whole grain cereal and complex carbohydrate intake. Arthritic patients may therefore be counselled to reduce their animal protein (arachidonic acid intake), to replace red meats with fish eg. flathead (increase their eicosapentaenoic acid), and to eat more spinach and beans (rich in linolenic acid). When selecting a polyunsaturated fat, arthritic patients should favour linseed, rich in linolenic acid, but not entirely exclude safflower or soyabean oils (rich in linoleic acid). By eating within contemporary nutritional guidelines it is possible to reduce the arachidonic acid concentration of the diet, increase omega-3 fatty acids and ensure adequate amounts of the essential linoleic acid. Exclusion of specific foodsubstances in an effort to eliminate food intolerance should only be implemented in selected cases who are screened for food reactions by implementing elimination and/or rotation diets. Dietary supplementation with Maxepa or an equivalent fatty acid source requires further research justification.

Concluding remarks

In including nutritional modification as a rheumatoid arthritis management strategy, the clinician is charged with the task of providing scientifically sound clinical intervention without denying the patient the potential benefit of an efficacious therapy. The aetiology and pathogenesis of rheumatoid arthritis remain controversial.[36] Metabolites of arachidonic acid metabolism, while being involved in inflammation, are only one of a number of inflammatory mediators.[37] Dietary therapy by means of altering arachidonic acid metabolism, like many other non-traditional treatments in the management of rheumatoid arthritis, remains unproven.[38] There is however, a measure of in vitro evidence which supports the hypothesis that alteration of arachidonic acid may be of benefit in this disabling disease. Clinicians are challenged by the need to neither succumb to the placebo nor the tomato effect.[39] While the placebo effect represents acceptance of useless and sometimes harmful therapies, the tomato effect involves nonrecognition and/or rejection of effective intervention techniques. Only appropriate clinical research can hope to adequately distinguish between these two phenomena.

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